Docket No.: 061404-0020 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	Customer Number: 20277
Donald J. KERRISH, et al.	:	Confirmation Number: 3590
Application No.: 10/765,134	:	Group Art Unit: 1623
Filed: January 28, 2004	:	Examiner: Lawrence E. Crane

For: PROCESS FOR PRODUCING WET RIBAVIRIN PELLETS

DECLARATION UNDER 37 C.F.R. § 1.132

1. I, Donald J. Kerrish, hereby declare and say as follows:

2. I am a co-inventor to the above-captioned application. I am currently employed by Three Rivers Pharmaceuticals, LLC, the assignee of the above-captioned application, and serve as President and CEO.

3. I received the degree of Bachelor of Science in Pharmacy in 1982 from Duquesne University, located in Pittsburgh, Pennsylvania. I have been formulating and compounding drugs for over thirty years and have been in the Pharmacy business for over thirty years. I have been studying ribavirin dosage forms for over ten years.

4. I have read and am familiar with the disclosure and presently pending claims of the above-captioned application.

5. The above-caption application discloses ribavirin compositions and methods for preparing ribavirin compositions. The disclosed methods include, for example, combining ribavirin with at least one excipient, such as a binder, to form a mixture and adding water to the ribavirin mixture to form ribavirin compositions.

6. The terms "excipient" and "binder" are understood by those skilled in the pharmaceutical art. These terms are commonly used throughout the pharmaceutical art.

7. Ribavirin has been known since the 1970's (see Merck Index attached hereto as Exhibit A). It is characterized as water-soluble and existing in one of two polymorphic forms. *Id.* It is reported that one of ribavirin's polymorphic forms has a melting point of 166-168 °C, which can be prepared by recrystallization from aqueous ethanol; and a second polymorphic form has a melting point of 174-176 °C, which can be prepared by recrystallization from ethanol. *Id.*

8. Ribavirin has been described as having poor processing characteristics, such as poor flow and low and variable tap density. See U.S. Patent 5,914,128 to Liebowitz et al. at column 1, lines 15-29. Liebowitz et al. further described the undesirability of creating polymorphic forms of ribavirin which may occur during processes to produce ribavirin compositions. See U.S. Patent 5,914,128 at column 1, lines 30-35. Liebowitz reported that it was surprising to prepare a ribavirin composition substantially free of polymorphic forms by dry compaction. See Liebowitz at column 3, lines 40-50. The conventional wisdom at the time of the Liebowitz publication was that certain processing steps, including heat generated from a compaction step, would result in the formation of undesirable polymorphic forms of ribavirin. *Id.*

9. Given the discussion in Liebowitz and that ribavirin is a water-soluble compound, it was surprising that ribavirin compositions can be prepared by adding water to a ribavirin mixture without creating polymorphs, i.e., without causing the ribavirin in the mixture to convert from one polymorphic form to another polymorphic form. Given the discussion in Liebowitz, it was further surprising that heating such a mixture did not create ribavirin polymorphs.

10. To determine whether a process for preparing a ribavirin composition created polymorphs, a differential scanning calorimetry (DSC) experiment was performed on a processed ribavirin composition using a MDSC 2920 (TA Instruments, New Castle, DE). For the DSC experiment, nitrogen was used as the purge gas at a flow rate of 50 ml/min for the DSC cell and 150 ml/min for the refrigerated cooling system. The calorimeter was calibrated for temperature and cell constant using indium (melting point 156.61 °C, enthalpy of fusion 28.71 J/g). The experiment was performed using non-hermetic aluminum pans. The sample was twice heated in the DCS with a heating and cooling rate of 10 °C/min.

11. A copy of two DSC traces are provided hereto as Exhibit B. The DSC traces were for a ribavirin composition prepared by adding water to a ribavirin mixture followed by heating the

wet mixture. The ribavirin initially used to prepare the formulation had a melting point of approximately 166-168 °C. The DSC data show a melting point for the ribavirin in the composition to be approximately 168 °C. There is no additional reasonably detectable melting point for the other polymorphic form of ribavirin at about 174-176 °C by DSC. Accordingly, the DSC results show that there was no evidence of a measurable polymorphic conversion. The fact that a ribavirin composition can be prepared by adding water to a ribavirin mixture without creating polymorphs was surprising. It was further surprising that a wet ribavirin mixture can be dried by heating without polymorphic change.

12. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful statement may jeopardize the validity of the application or any patent issued thereon.

Donald J. Kerrish

Donald J. Kerrish

6-OCT-2008

Date

WDC99 1276536-2.061404.0020

EXHIBIT A

THE MERCK INDEX

AN ENCYCLOPEDIA OF
CHEMICALS, DRUGS, AND BIOLOGICALS

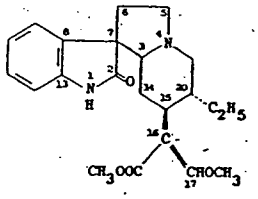
ELEVENTH EDITION

Susan Budavari, *Editor*
Maryadele J. O'Neil, *Associate Editor*
Ann Smith, *Assistant Editor*
Patricia E. Heckelman, *Editorial Assistant*

Published by
MERCK & CO., INC.
RAHWAY, N.J., U.S.A.

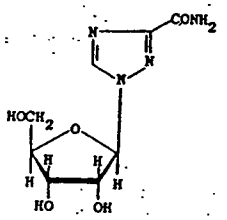
1989

Pharm. Bull. 11, 441, 446, 451 (1963). Partial synthesis: Finch, Taylor, *J. Am. Chem. Soc.* 84, 1318, 3871 (1962). Total synthesis: Ban *et al., Tetrahedron Letters* 1972, 2113.



Crystals from methanol, mp 216°; *dl*-form reported as colorless pillars from ethyl acetate-ether, mp 197-199° (Ban *et al., loc. cit.*). $[\alpha]_D^{13}$ −14.7° (c = 2.5 in chloroform). pKa 6.4. uv max: 245, 280 nm (log ε 4.24, 3.15). Sol in chloroform; moderately sol in acetone, alcohol, benzene; sparingly sol in ether, ethyl acetate. Practically insol in petr ether.

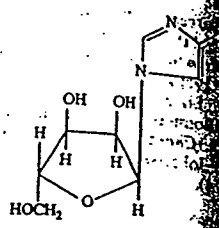
8199. Ribavirin. *1-β-D-Ribofuranosyl-1H-1,2,4-triazole-3-carboxamide;* ICN-1229; RTCA; Viramid; Virazid; Virazole. $C_8H_{12}N_4O_5$; mol wt 244.21. C 39.34%, H 4.95%, N 22.94%, O 32.76%. The first synthetic, non-interferon-inducing, broad-spectrum antiviral nucleoside. Preliminary information: *Chem. & Eng. News* 50, 26 (April 17, 1972). Synthesis: J. T. Witkowski *et al.*, 163rd Am. Chem. Soc. Meeting (Boston, April 1972), *Abstracts of Papers* MEDI 19; *eidem, J. Med. Chem.* 15, 1150 (1972); *eidem, J. Carbohyd. Nucl. Nucl.* 5, 363 (1978). Regioselective synthesis: Y. Ito *et al., Tetrahedron Letters* 1979, 2521; R. R. Schmidt, D. Heermann, *Ber.* 114, 2825 (1981). Structure and conformation studies: Kreishman *et al., J. Am. Chem. Soc.* 94, 5894 (1972); Prusiner, Sundaralingam, *Nature New Biol.* 244, 116 (1973). Activity studies: Sidwell *et al., Science* 177, 705 (1972); Huffman *et al., Antimicrob. Ag. Chemother.* 3, 235 (1973); Sidwell *et al., ibid.* 242; Khare *et al., ibid.* 517. *In vitro* inhibition of HIV-1 (HTLV-III/LAV) virus replication: J. B. McCormick *et al., Lancet* 2, 1367 (1984). Toxicity data: J. T. Witkowski *et al., J. Med. Chem.* 15, 1150 (1972). Teratogenicity studies: V. H. Ferm *et al., Teratology* 17, 93 (1978); D. M. Kochhar *et al., Toxicol. Appl. Pharmacol.* 52, 99 (1980). Controlled clinical trial in infants with respiratory syncytial viral infection: C. B. Hall *et al., N. Engl. J. Med.* 308, 1443 (1983); in Lassa fever: J. B. McCormick *et al., ibid.* 314, 20 (1986). *Review:* R. Sidewell *et al., Pharmacol. Ther.* 6, 123-146 (1979); F. E. Hahn, Ed. in *Antibiotics* vol. 5, pt. 2 (Springer-Verlag, New York, 1979) pp 439-458.



Colorless, water-soluble, stable material. Exists in two polymorphic forms: mp 166-168° (aq ethanol); mp 174-176° (ethanol). $[\alpha]_D^{25}$ −36.5°. LD_{50} i.p. in mice: 1.3 g/kg; orally in rats: 5.3 g/kg (Witkowski).

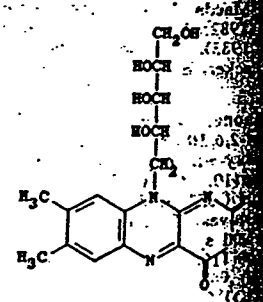
THERAP CAT: Antiviral.

8200. α-Ribazole. *5,6-Dimethyl-1-α-D-ribofuranosyl-1H-benzimidazole.* $C_{14}H_{18}N_2O_4$; mol wt 278.31. C 60.42%, H 6.52%, N 10.07%, O 22.99%. Nucleoside moiety of vitamin B_{12}, *q.v.* Isoln by acid hydrolysis of vitamin B_{12}: N. G. Brink *et al., J. Am. Chem. Soc.* 72, 1866 (1950); N. G. Brink, K. Folkers, *ibid.* 74, 2856 (1952). Syntheses of α- and β-anomers: F. W. Holly *et al., ibid.* 4521; R. S. Wright *et al., ibid.* 80, 2004 (1958); J. D. Stevens *et al., J. Org. Chem.* 33, 1806 (1968). Biosynthetic study: J. Hörig, P. Renz, *FEBS Letters* 80, 337 (1977). Spectroscopic characterization: K. L. Brown *et al., Inorg. Chem.* 23, 1463 (1984).



Crystals from water, mp 198-199° (pyridine).

8201. Riboflavine. Vitamin B_2; 7,8-dimethyl-10-(D-*ribo*-2,3,4,5-tetr... loxazine; 7,8-dimethyl-10-ribityli... Flavaxin; Ribipca. $C_{17}H_{20}N_4O_6$; mp... H 5.36%, N 14.89%, O 25.51%. Ne... milk, eggs, malted barley, liver, kidn... bles. Richest natural source is yeast... ent in all plant and animal cells... only in the retina of the eye, in whey... forms occurring in tissues and cells... *tide (FMN, riboflavine-5-phosphate)... nucleotide (FAD).* First syntheses: K... *Acta* 18, 426, 522 (1935); Kuhn *et... (1935). Riboflavin for therapeutic... thesis, the most common starting ma... D-ribose, and alloxan. Improved ky... U.S. pat. 2,807,611 (1957 to Mer... synthesis: F. Yoneda *et al., J. Chem... 1978, 348. Several fermenting organ... *gossypii* and *Eremothecium ashbyii*, ha... thesize large quantities of riboflavin... try and livestock feeds are produce... process. Example of production by... *gossypii*): Malzahn *et al.*, U.S. pat. 2... Processing Corp.). Early reviews: ... *mins* (New York, 1945); Sebrell, ... III (Academic Press, New York, 1... Knobloch, *Chemie und Technik der... (Enke, Stuttgart, 1955). Review of me... *Engl. J. Med.* 283, 463 (1970). Re... assay methods: Pearson, *The Vitamins*... W. N. Pearson, Eds. (Academic Pres... 1967) pp 99-136. Comprehensive re... 1-96 (1972).



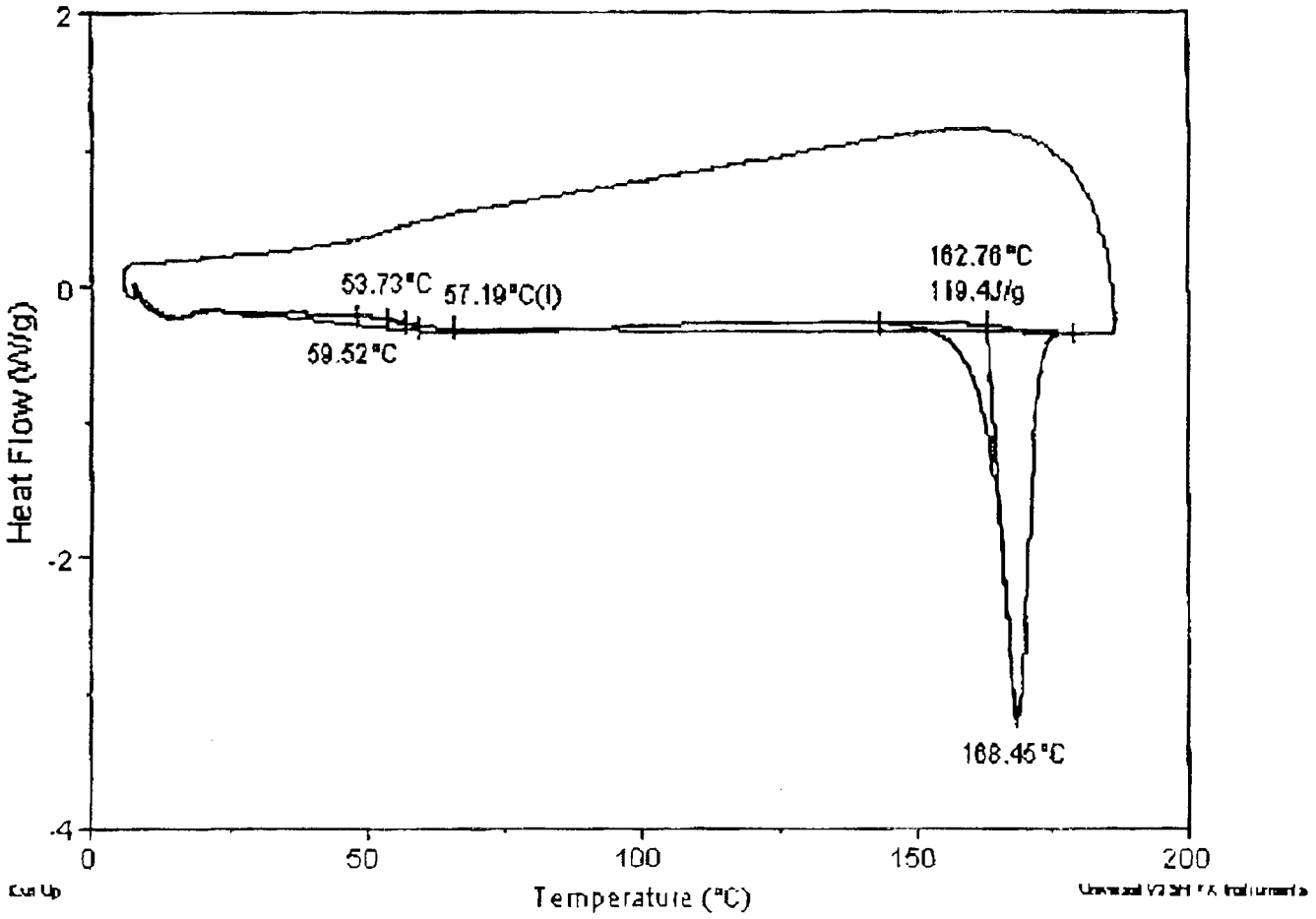
Fine orange-yellow needles from ... water, or pyridine. Dec at 278-282° (dar... Three different crystal forms having d... water: Dale, U.S. pats. 2,603,633 and ... it is not appreciably affected by diffuse... soln it deteriorates quite rapidly, the d... celerated by light. $[\alpha]_D^{25}$ −112° to −... 0.1*N* alcoholic NaOH dil to 10 ml with... max: 220-225, 266, 371, 444, 475 nm... in from 3000 to about 15,000 ml of w... the soly being due to differences in th... Slightly more sol in NaCl solns; less s... water (0.0045 g/100 ml of abs ethanol)... sol in cyclohexanol, amyl acetate, ben... insol in ether, chloroform, acetone, be...

EXHIBIT B

Sample: Ribavarin 8 (tablet)
Size: 7.5700 mg

DSC

File: C:...\DSC\UPM\Rib0116.003
Operator: Nasser
Run Date: 16-Jan-01 17:04



Sample: Ribavarin 0 (tablet)
Size: 7.7100 mg

DSC

File: C:...\DSC\UPMARib0118.004
Operator: Nasser
Run Date: 18-Jan-01 15:38